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Endocrine and Metabolic Responses in Children with Meningoccocal Sepsis: Striking Differences between Survivors and Nonsurvivors

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ABSTRACT

To get insight in the endocrine and metabolic responses in children with meningococcal sepsis 26 children were studied the first 48 h after admission. On admission there was a significant difference in cortisol/ACTH levels between nonsurvivors (n = 8) and survivors (n = 18). Nonsurvivors showed an inadequate cortisol stress response in combination to very high ACTH levels, whereas survivors showed a normal stress response with significantly higher cortisol levels (0.62 *vs.* 0.89 μmol/L) in combination with moderately increased ACTH levels (1234 *vs.* 231 ng/L). Furthermore, there was a significant difference between nonsurvivors and survivors regarding pediatric risk of mortality score (31 *vs.* 17), TSH (0.97 *vs.* 0.29 mE/L), T_3 (0.53 *vs.* 0.38 nmol/L), reverse T_3 (rT_3) (0.75 *vs.* 1.44 nmol/L), C-reactive protein (34 *vs.* 78 mg/L), nonesterified fatty acids (0.32 *vs.* 0.95 mmol/L), and lactate (7.3 *vs.* 3.2 mmol/L). In those who survived, the most important changes within 48 h were seen in a normalization of cortisol and ACTH levels, but without a circadian rhythm; a decrease of rT_3 and an increase in the T_3/rT_3 ratio; and a decrease in the levels of the nonesterified free fatty acids and an unaltered high urinary nitrogen excretion. At this moment, it is yet unknown whether the hormonal abnormalities are determining factors in the outcome of acute meningococcal sepsis or merely represent secondary effects. Understanding the metabolic and endocrine alterations is required to design possible therapeutic approaches. The striking difference between nonsurvivors and survivors calls for reconsideration of corticosteroid treatment in children with meningococcal sepsis. (*J Clin Endocrinol Metab* **85:** 3746–3753, 2000)

SEPTIC SHOCK WITH purpura is a life-threatening clinical syndrome predominantly caused by *Neisseria meningitidis* and characterized by a sudden onset and rapid progression of disease. The physiological changes that constitute the process of sepsis are induced by microbial agents during bloodstream infection or by the toxic products of pathogens that are released from sites of focal infection. This process involves changes generated by the immune system in which hormones, cytokines, and enzymes are involved.

In adult patients it has been shown that sepsis may lead to pronounced neuro-endocrine and metabolic alterations including increased serum cortisol concentrations; low thyroid hormones; insulin resistance; elevations of plasma glucose, lactate, and free fatty acid concentrations; and increased muscle protein breakdown (1–4). During the time course of sepsis an ebb and flow phase can be detected. Main features in the ebb phase are a decrease in metabolic rate and temperature, and in the flow phase there is an increase in metabolic rate and urinary nitrogen excretion (5, 6). There are several differences between the host response of young children compared with adults during meningococcal sepsis (7). Little is known about the neuro-endocrine changes in critically ill infants and children. Previous studies in critically ill infants and children showed an altered thyroid function at the onset of acute diseases called "the euthyroid sick syndrome" (8–12). Dopamine infusion induces or aggravates partial hypopituitarism in newborn infants, resulting in inhibited PRL and GH secretion (8). The present study was undertaken to evaluate the time course of the endocrine and metabolic responses of children with meningococcal sepsis during the first 48 h of admission in the pediatric intensive care unit (PICU).

Materials and Methods

Study protocol

Children above 3 months and below 18 yr of age with septic shock and petechiae/purpura requiring intensive care treatment were enrolled in this study. The group consisted of children primary admitted or referred to the PICU of the Sophia Children's Hospital between October 1997 and October 1998. Patients were eligible for inclusion when they met the following criteria: 1) presence of petechia/purpura; and 2) presence of shock for less than 6 h, defined as persistent hypotension (systolic blood pressure <75 mm Hg for children between 3 and 12 months, <80 mm Hg for 1–5 yr, <85 mm Hg for 6–12 yr, <100 mm Hg for children older than 12 yr), or evidence of poor end-organ perfusion, defined as at least two of the following: unexplained metabolic acidosis (pH <7.3 or base excess less than −5 mmol/L or plasma lactate levels >2.0 mmol/L); arterial hypoxia (PO_2 <75 mm Hg, a PO_2/FiO_2 ratio <250, or transcutaneous oxygen saturation <96%) in patients without

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overt cardiopulmonary disease; acute renal failure (diuresis <0.5 mL/kg·h for at least 1 h despite acute volume loading or evidence of adequate intravascular volume without preexisting renal disease); or sudden deterioration of the baseline mental status. The patients participated in a randomized, double-blinded, dose-finding study of protein C concentrate (human; Immuno-Baxter, Vienna, Austria). Because protein C is assumed not to influence the endocrine and metabolic assays and did not influence mortality we did not account for it in further analysis. The Medical Ethics Committee of the Erasmus University Rotterdam approved the study protocol. Informed consent was obtained from the parents or legal representatives.

Clinical parameters

The pediatric risk of mortality (PRISM II) score was calculated based on the most abnormal values regarding 14 physiological variables during the first 6 h of admission. A higher score means a higher risk of mortality (13–15). The interval between appearance of petechiae and admission to the PICU, length of stay in the PICU, and duration of inotropic support were recorded. To distinguish nonsurvivors from survivors established parameters to monitor the severity of disease, such as PRISM, lactate, and C-reactive protein (CRP) were analyzed (14, 15).

Collection of blood

Arterial blood samples were collected within 2 h after admission (T = 0), after 24 h (T = 24), and 48 h (T = 48) for determination of thyroid hormones, insulin, glucose, pre-albumin, CRP, nonesterified free fatty acids (NEFAs), and lactate. Blood samples for cortisol and ACTH were taken at T = 0 and 12 h (T = 12) after admission. An ACTH test was not performed because all children had severe stress due to the life-threatening disease on admission. A diurnal rhythm for cortisol and ACTH was estimated by sampling blood on the second day of admission at 0800 h and subsequently at 1400 and 2000 h.

Hormonal assays

Cortisol/ACTH. The plasma concentrations of cortisol were measured by competitive luminescence immunoassay. The detection limits were 0.03–1.38 μmol/L. The plasma concentrations of ACTH were measured by immunoradiometric assay (ELSA-ACTH; CIS-Bio International, Gif-suryvette, France), using two monoclonal antibodies. The within-run coefficients of variation were 6.1% at 22 pg/mL, 2.9% at 59 pg/mL, and 2.1% at 778 pg/mL. The between-run coefficients of variation were 5.3% at 40 pg/mL, 4.8% at 203 pg/mL and 1.3% at 1055 pg/mL. The reference values for cortisol were: 0800 h, 0.2–0.6 μmol/L; 1400 h, 0.1–0.5 μmol/L; and 2000 h, 0.05–0.3 μmol/L. The reference value for ACTH was 20–100 ng/L. From the values of cortisol and ACTH the cortisol/ACTH ratio was calculated.

Thyroid hormones. Plasma T_4, T_3, and reverse T_3 (rT_3) were measured by established RIA procedures, as described previously (16, 17). The reference values of the laboratory were: T_4, 64–132 nmol/L; T_3, 1.1–2.6 nmol/; and rT_3, 0.15–0.43 nmol/L. From the values of T_3 and rT_3 the T_3/rT_3 ratio was calculated. The plasma concentrations of free T_4 (fT_4) were measured by a direct, labeled antibody, competitive immunoassay technique (Amerlite MAB fT_4 Assay; Ortho-Clinical Diagnostics, Strassbourg, France). The within-assay coefficients of variation were 7.6% at 5.43 pmol/L, 4.3% at 16.1 pmol/L, and 3.5% at 52.8 pmol/L. The between-assay coefficients of variation were 9.0% at 5.67 pmol/L, 5.6% at 17.4 pmol/L, and 4.2% at 49.2 pmol/L. The reference value for fT_4 was 11–25 pmol/L.

The plasma concentrations of *TSH* were measured by an ultrasensitive immunometric assay (Amerlite TSH-30; Ortho-Clinical Diagnostics), using one monoclonal antibody. The within-assay coefficients of variation were 8.0% at 0.087 mIU/L, 4.2% at 4.22 mIU/L, and 4.1% at 21.5 mIU/L. The between-assay coefficients of variation were 11.7% at 0.077 mIU/L, 6.6% at 4.25 mIU/L, and 5.1% at 21.4 mIU/L. The reference value for TSH was less than 4.5 mE/L.

Insulin/glucose. Insulin was measured in serum with an immunoradiometric assay. The detection limit was 5–400 mU/L. Glucose measurements were determined on the routine clinical chemistry analyzers (Dimension ES; Dupont Medical Products, Wilmington, DE) (reference values: hypoglycemia, <2.6 mmol/L; hyperglycemia, >11 mmol/L). From the values of insulin and glucose the insulin to glucose ratio was calculated.

Metabolic assays

Lactate was measured by enzymatic end point determination (Hitachi 911; Roche Molecular Biochemicals, Mannheim, Germany) (normal, <2.0 mmol/L). CRP was determined by an immunonephelometric assay (normal, <5 mg/L) (18). Plasma NEFA concentrations were determined by the enzymatic method (Nefac-kit; Wako, Instruchemie BV, Neuss, Germany). The reference values for NEFAs were: children between 4 months and 10 yr, 0.3–1.1 mmol/L; children more than 10 yr, 0.2–0.8 mmol/L.

Urinary nitrogen excretion

Urine was collected daily for 24 h and analyzed for urinary nitrogen. Total urinary nitrogen excretion was defined as 1.25× urinary urea nitrogen, to adjust for the urinary nitrogen loss as ammonia, creatinine, and uric and amino acids (19). No correction was made for nitrogen losses through stools, skin, wounds, nasogastric suction, or blood sampling.

Caloric intake

The patients were fed enteral and/or parenteral according to a standard feeding protocol. During the stay in the PICU glucose was administered at a rate of ~4–6 mg/kg·min. If enteral feeding could not be started on the second day, parenteral feeding was started. The initial dose of proteins was 1.0 g/kg·day (Aminovenös N-paed 10%; Fresenius, 's-Hertogenbosch, Holland) and of lipids (in case the body temperature was <38.5 C) was 1.0 g/kg·day (Intralipid 20%; Pharmacia & Upjohn, Inc., Woerden, Holland). If clinically possible, enteral and/or parenteral nutrition was adjusted on days 3 and 4 to normal needs for healthy children. The total caloric intake was recorded and calculated daily. The amount of caloric intake was corrected for extra protein calories such as plasma and/or albumin infusions. To estimate the adequacy of caloric intake, the amount of energy intake was compared with calculated values for resting energy expenditure for healthy children according to the formula of Schofield (20) for age, sex, and weight.

Statistics

Statistical analysis was performed with a statistical analysis software program (SPSS 7.0 for Windows 95; SPSS, Inc., Chicago, IL). The results are expressed as medians (interquartiles), unless specified otherwise. The Mann-Whitney *U* test was used for comparison of clinical and laboratory tests between survivors and nonsurvivors. For survivors, the Wilcoxon signed rank test was used for comparison on different time points of different laboratory tests. Spearman's correlation coefficient (r) was used to evaluate the relationship between different parameters. Two-tailed *P* values of 0.05 or less were considered statistically significant.

Results

Demographics

Twenty-six patients admitted to the PICU fulfilled the inclusion criteria and were included in the study; there were 16 males and 10 females (Table 1). The median age was 23 months (range, 4–185). Cultures of blood revealed *Neisseria meningitidis* in all 26 patients.

Clinical parameters

Eight children died after a median stay in the PICU for 10 h (range, 2–40); eighteen children survived, and they stayed in the PICU for a median of 86 h (range, 30–312). There was a significant difference in age between nonsurvivors and survivors (10 *vs.* 29 months, $P < 0.05$). The interval between

appearance of petechiae and admission to the PICU was 5.8 h (range, 2.5–18.). There was a significant difference between nonsurvivors and survivors for the interval between appearance of petechiae and admission to the PICU (3.5 *vs.* 7.0 h, $P < 0.05$). Concomitant therapy during the study period included antibiotics, administration of plasma, and inotropics for all patients [10 patients received dopamine, 22 received noradrenaline, and 25 received dobutamine (24 patients received a combination of inotropics)]. Nonsurvivors received significantly higher doses of inotropics (dobutamine and noradrenaline, $P < 0.01$). The 18 survivors received inotropic therapy for a median of 49 h (range, 9–170). Administration of corticosteroids is not a routine procedure in The Netherlands. For that reason, none of the children received corticosteroid therapy on admission. Seventeen patients required mechanical ventilatory support and sedation with benzodiazepines. The parameters to monitor severity of disease were significantly different between nonsurvivors and survivors [PRISM score (31 *vs.* 17, $P < 0.01$); arterial lactate levels (7.3 *vs.* 3.2 mmol/L, $P < 0.01$; Fig. 1); and CRP levels (34 *vs.* 78 mg/L, $P < 0.01$)] (Table 2). In survivors, compared with levels on admission, lactate levels decreased significantly after 24 and normalized after 48 h, and CRP levels were significantly increased after 24 and 48 h.

TABLE 1. Endocrine and metabolic parameters on admission

Age (months)	Sex	Duration of petechiae before admission (h)	PRISM score	Survival
4	M	7	12	Yes
5	M	3.5	30	No
5.5	M	3	34	No
7	F	4	32	No
9	F	3.5	19	No
10	F	9	16	Yes
10	M	7	32	No
12	F	9	18	Yes
15	F	4	18	Yes
18	M	5.5	27	Yes
19	M	1	15	Yes
21	M	15	18	Yes
21	M	8	29	No
24	M	0.5	37	No
25	M	15	21	Yes
27	F	10	14	Yes
30	M	3	24	Yes
32	F	6	10	Yes
52	F	9	20	Yes
77	M	7	15	Yes
81	F	11	7	Yes
113	M	3.5	29	No
128	M	4	9	Yes
136	M	4	24	Yes
141	M	10	24	Yes
185	F	6	14	Yes

M, Male; F, female; PRISM score, pediatric risk of mortality score.

Cortisol/ACTH

On admission, nonsurvivors had significantly lower serum cortisol levels than survivors (0.62 *vs.* 0.89 μmol/L, $P < 0.05$), whereas the ACTH levels were extremely high in those who did not survive (1234 *vs.* 231 ng/L, $P < 0.01$) (Table 2 and Fig. 2). The cortisol/ACTH ratio was significantly different between nonsurvivors and survivors ($P < 0.01$). ACTH and the cortisol/ACTH ratio correlated well with parameters to monitor the severity of disease (PRISM, lactate, and CRP) (Table 3). In those who survived 12 h after admission levels of cortisol (0.73 μmol/L) and ACTH (31 ng/L) decreased significantly in comparison with levels on admission; on the second day after admission there was a further significant decrease of levels of cortisol (0.54 μmol/L) and ACTH (18 ng/L) in comparison with levels on admission and the levels of 12 h after admission (Table 2). In 14 survivors, on day 2, a cortisol/ACTH profile was performed; in none of them could a circadian rhythm be detected in the three samples taken at 0800, 1400, and 2000 h.

TABLE 2. Endocrine and metabolic differences between survivors and nonsurvivors on admission and time course of survivors

	Nonsurvivors	Survivors			Normal reference
	T = 0	T = 0	T = 24[a]	T = 48	
PRISM	31 (29–34)	17 (14–17)[b,c]			
Cortisol, μmol/L	0.62 (0.49–0.79)	0.89 (0.77–1.15)[b,c]	0.54 (0.38–0.62)[d,c]		0.2–0.6
ACTH, ng/L	1234 (740–2915)	231 (48–665)[b,c]	18 (12–31)[d,c]		20–100
Cortisol/ACTH	0.58^{-3} (0.17^{-3}–1.00^{-3})	6.1^{-3} (1.8^{-3}–21.7^{-3})[b,c]	29^{-3} (17^{-3}–34^{-3})[d,c]		
TSH, mE/L	0.97 (0.52–1.56)	0.29 (0.15–0.54)[b,c]	0.55 (0.17–1.80)	1.73 (0.36–2.41)[c,e]	<4.5
T_4, nmol/L	38 (25–46)	44 (39–56)	49 (38–64)	45 (34–71)	64–132
T_3, nmol/L	0.53 (0.43–0.76)	0.38 (0.26–0.42)[b,f]	0.58 (0.27–0.85)[d,c]	0.63 (0.29–0.97)[e,f]	1.1–2.6
rT_3, nmol/L	0.75 (0.55–0.97)	1.44 (0.99–1.85)[b,c]	1.52 (1.29–2.21)	0.98 (0.75–1.35)[e,f,g,c]	0.15–0.43
T_3/rT_3	0.76 (0.64–0.85)	0.43 (0.17–0.35)[b,c]	0.43 (0.13–0.62)	0.87 (0.21–1.14)[e,f,g,c]	
fT_4, pmol/L	14 (13–21)	16 (15–19)	13 (12–19)	12 (9–19)[c,e]	11–25
Insulin, mU/L	5 (5–7)	13 (5–21)[b,c]	16 (10–29)	19 (12–29)[e,f]	
Glucose, mmol/L	3.9 (2.5–6.5)	6.3 (5.2–7.8)[b,f]	6.0 (5.7–8.0)	6.5 (5.5–7.2)	2.6–11
Insulin/glucose	1.8 (0.9–2.0)	1.8 (1.1–2.6)	2.7 (1.7–4.0)	3.1 (2.1–3.5)[e,f]	<50
CRP, mg/L	34 (24–37)	78 (58–100)[b,c]	201 (172–244)[d,c]	165 (133–219)[c,e]	<5
Lactate, mmol/L	7.3 (5.9–10.4)	3.2 (2.2–5.1)[b,c]	2.0 (1.5–2.8)[d,f]	1.5 (1.2–2.0)[c,e]	<2.0
NEFA, mmol/L	0.32 (0.25–0.50)	0.95 (0.7–1.4)[b,c]	0.73 (0.46–0.84)[d,f]	0.41 (0.28–0.77)[c,e]	0.3–1.1

[a] For cortisol and ACTH T = 24 is 0800 h day 2.
[b] Significant difference between nonsurvivors and survivors.
[c] All values are expressed as median and interquartiles, $P < 0.01$.
[d] Significant difference between T = 24 and T = 0.
[e] Significant difference between T = 48 and T = 0.
[f] All values are expressed as median and interquartiles, $P < 0.05$.
[g] Significant difference between T = 48 and T = 24.

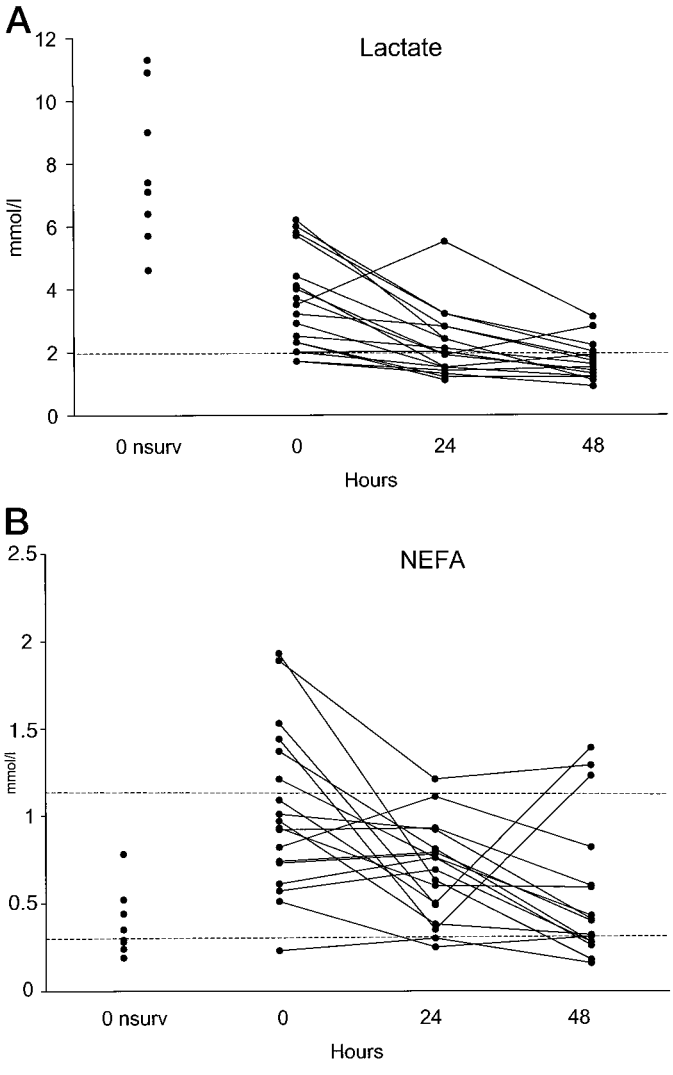

FIG. 1. Levels of lactate (A) and NEFA (B) on admission for nonsurvivors (0 nsurv) and survivors (0) and the time course of these levels for survivors after 24 and 48 h. Reference values below or between *dotted lines*.

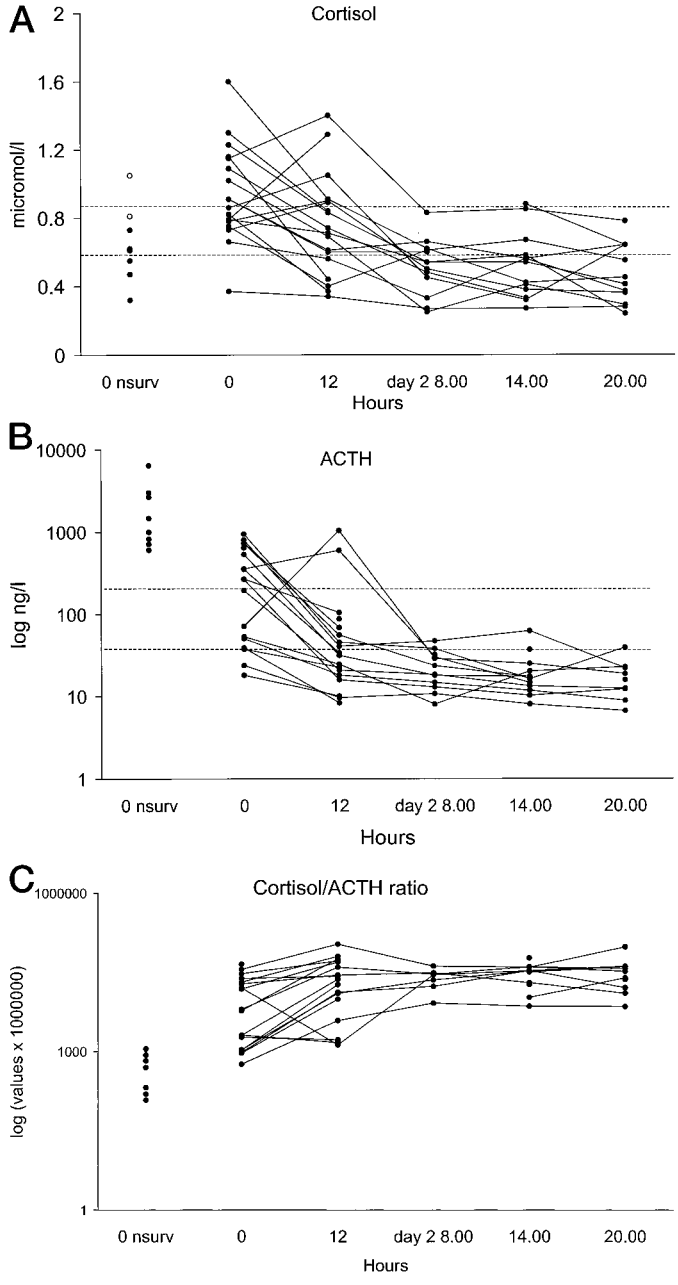

FIG. 2. Levels of cortisol (A), ACTH (B), and the cortisol/ACTH ratio (C) on admission for nonsurvivors (0 nsurv) and for survivors (0) and the time course for survivors after 12 h and on day 2 at 0800 h, 1400 h, and 2000 h. Reference values between *dotted lines*.

Thyroid hormones

On admission, data of nonsurvivors and survivors showed significant differences in levels of rT_3 (0.75 *vs.* 1.44 nmol/L, $P < 0.01$), the T_3/rT_3 ratio (0.76 *vs.* 0.43, $P < 0.01$), TSH (0.97 *vs.* 0.29 nmol/L, $P < 0.01$), and T_3 (0.53 *vs.* 0.38 nmol/L, $P < 0.05$), whereas the levels of T_4 and fT_4 were not significantly different between the two groups (Table 2 and Fig. 3). In comparison with normal reference values, the levels of T_4 and T_3 were decreased in both nonsurvivors and survivors, and those of rT_3 were increased. The median fT_4 and TSH levels were within the normal reference range. On admission, there were, except for fT_4, significant correlations between levels of TSH, T_3, rT_3, and the T_3/rT_3 ratio with the parameters to monitor the severity of disease (Table 3). After 48 h survivors showed significantly increased levels of TSH, T_3, and the T_3/rT_3 ratio and significantly decreased levels of rT_3 and fT_4 in comparison with levels on admission, whereas the level of T_4 did not change significantly. For survivors 48 h after admission median levels of T_3, T_4, and rT_3 remained below normal reference values, whereas median fT_4 and TSH levels remained within the normal reference values (Fig. 2).

Insulin/glucose

On admission, nonsurvivors showed significantly different levels of insulin (5 *vs.* 13 mU/L, $P < 0.05$) and glucose (3.9 *vs.* 6.3 mmol/L, $P < 0.05$) compared with survivors (Table 2 and Fig. 4). The insulin to glucose ratio did not show statistical significance between survivors and nonsurvivors (Table 2). On admission, two of the children had a hypoglycemia

TABLE 3. Nonlinear significant correlation-coefficients (Spearman) between endocrine parameters, NEFA, and parameters to monitor severity of disease (lactate, CRP, and PRISM score) on admission

	Lactate	CRP	PRISM
Cortisol	−0.40[a]	0.10	−0.37
ACTH	0.57[a]	−0.64[b]	0.68[b]
Cort/ACTH	−0.63[b]	0.54[a]	−0.64[b]
TSH	0.53[b]	−0.43[a]	0.42[a]
T_4	0.07	0.06	−0.34
T_3	0.45[a]	−0.49[a]	0.29
rT_3	−0.34	0.48[a]	−0.41[a]
T_3/rT_3	0.42[a]	−0.51[a]	0.35
fT_4	0.40	−0.17	−0.41
Insulin	−0.09	0.18	−0.35
Glucose	−0.23	0.15	−0.36
Insulin/glucose	0.19	0.04	−0.06
NEFA	−0.47[a]	0.32	−0.48[a]

[a] $P < 0.05$.
[b] $P < 0.01$.

(2.4 and 1.6 mmol/L) and two children had a hyperglycemia (11.6 and 14.3 mmol/L). After 48 h survivors showed significantly increased levels for insulin and the insulin to glucose ratio in comparison with levels on admission, whereas the levels of glucose showed no changes (Fig. 4). There were no significant correlations between insulin, glucose and the insulin to glucose ratio *vs.* the levels of cortisol and the parameters to monitor the severity of disease (Table 3).

NEFAs

On admission, nonsurvivors had significantly lower NEFA levels than survivors (0.32 *vs.* 0.95 mmol/L, $P < 0.01$) (Table 2 and Fig. 1). Median NEFA levels for both nonsurvivors and survivors remained within normal reference values on admission. NEFA levels decreased significantly after 48 h in comparison with the levels of admission and after 24 h. Levels of NEFA correlated negatively with lactate and PRISM score ($P < 0.01$) (Table 3).

Nitrogen excretion

Nitrogen excretion was assessed in 16 survivors. The median nitrogen excretion was not significantly different between the first 24 h and the second 24 h after admission 271 mg/kg·day (range, 64–940) *vs.* 251 mg/kg·day (range, 152–737).

Caloric intake

For survivors, the median difference between actual energy intake and calculated resting energy expenditure was −45% (range, −83% to 24%) during the first 24 h after admission and −42% (range, −83% to 27%) during the second 24 h after admission.

Time course in nonsurvivors

Six of the eight nonsurvivors died within 14 h because shock persisted in all; in two of these six children it was combined with pulmonary edema, in one child with convulsions, in one child with pulmonary hypertension, and in one child with cerebral death. Two children died after 24 h (25 and 40 h). For these children, the interval between appearance of petechiae and admission to the PICU was significantly longer (7 and 8 h) compared with the other six children [median, 3.5 h (range, 0.5–4. h; $P < 0.05$)]. These two children also showed higher cortisol levels on admission (0.73 and 1.05 μmol/L; Fig. 2, ○) than the other six children. After 24 h both children showed decreased levels of ACTH, but these levels still remained above normal reference values (163 and 805 ng/L). In one of these two children a cortisol measurement was done after 24 h, showing only a slight improvement of the level of cortisol (from 0.73 to 0.80 μmol/L) in view of the ultimate state of stress. Furthermore, both children showed after 24 h an increase in rT_3 levels (from 0.95 to 1.65 nmol/L) and CRP (from 34 to 111 mg/L). The level of lactate, however, increased in both children. In the child who lived for 40 h shock persisted, recurrent convulsions developed, and severe bradycardias occurred a few hours before death. In the child who lived for 25 h shock persisted, and a combination with severe pulmonary hypertension lead to death.

Discussion

Our study shows that children who do not survive meningococcal sepsis have an impaired adrenal response, altered thyroid hormones, and decreased levels of NEFAs, associated with a higher severity of disease score on admission. The observed endocrine and metabolic changes are of such clinical importance to reconsider therapeutic strategies.

One of the most striking alterations in our study concerned a significant difference in cortisol/ACTH response between nonsurvivors and survivors on admission. Nonsurvivors showed an inadequate cortisol response in combination with very high ACTH levels, whereas survivors showed a normal stress response with significantly higher cortisol levels in combination with moderately increased ACTH levels. ACTH and the cortisol/ACTH ratio were strongly correlated with survival and parameters to monitor the severity of disease. Low cortisol levels in nonsurvivors and high cortisol levels in survivors have been reported in the past in children with meningococcal sepsis (21, 22). More recently, only one other study in children with meningococcal sepsis reported the levels of ACTH in relation with the levels of cortisol. Significantly higher ACTH levels were found in those who died (23). The decreased production of cortisol in relation with high levels of ACTH might be caused by various mechanisms. First, the low production of cortisol might be the result of bilateral adrenal hemorrhages [described previously as the Waterhouse-Friderichsen syndrome (21, 22)], due to severe coagulation disorders found in meningococcal sepsis (15). Second, alternatively, an inadequate perfusion of the adrenal cortex due to hypotension might have lead to impaired adrenal function with diminished cortisol production. Our study seems to support this mechanism because we found a strong negative correlation between levels of cortisol and lactate. Third, in the presence of higher levels of endotoxin and tumor necrosis factor α (as seen in nonsurvivors), there might be a decreased adrenal ACTH receptor binding and a suppressed synthesis of cortisol (24, 25). Salem *et al.* (26) reported a family of peptides (called corticostatins) that

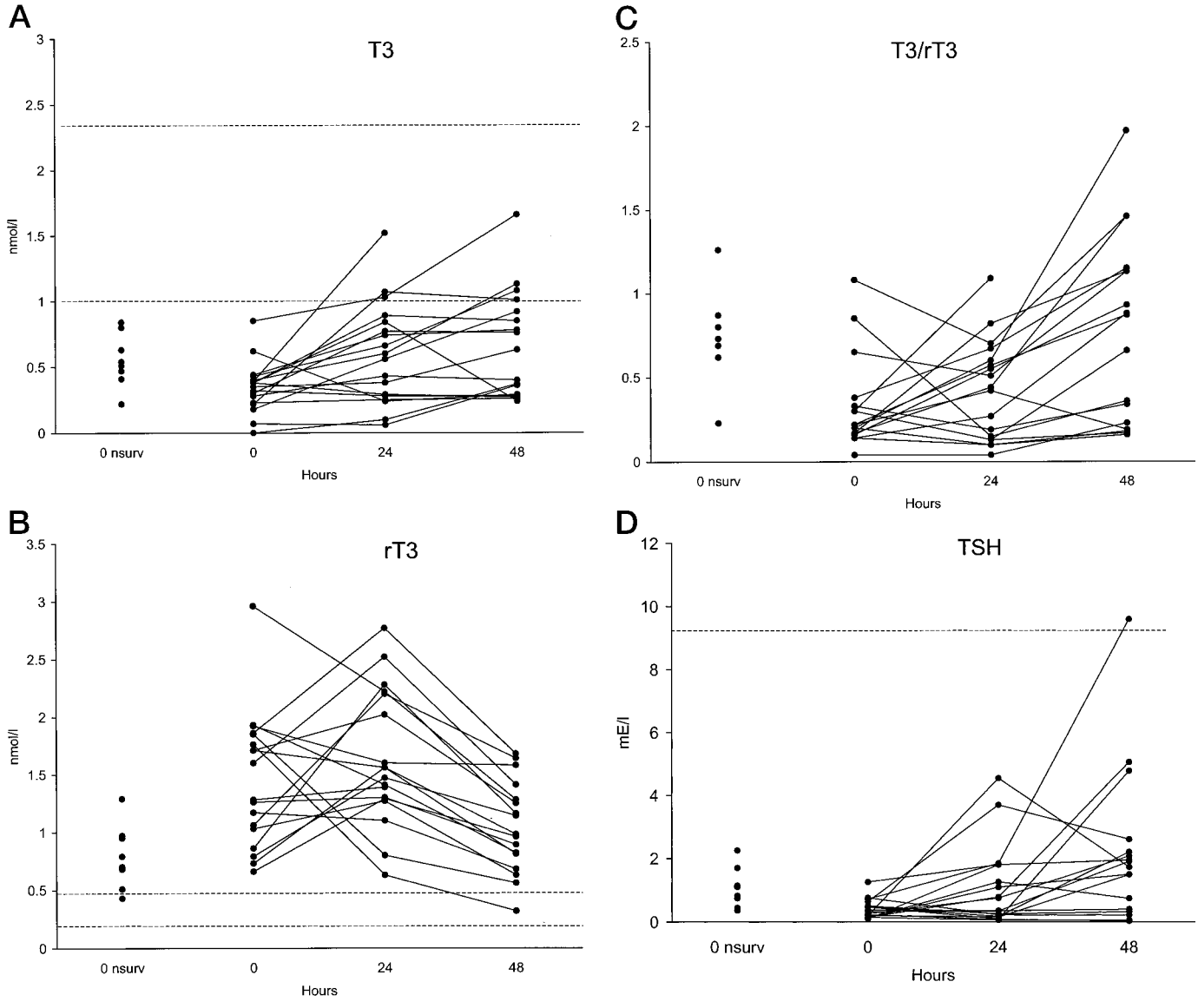

FIG. 3. Levels of T_3 (A), rT_3 (B), TSH (D), and ratio T_3/rT_3 (C) on admission for nonsurvivors (0 nsurv) and for survivors (0) and the time course of these levels for survivors after 24 and 48 h. Reference values below or between *dotted lines*.

might impair the sensitivity of the adrenals to ACTH during sepsis. It remains a question whether treatment with supplemental steroids, which is not a routine treatment in The Netherlands, will be beneficial (27). In our study, there was a very rapid and aggressive course of the disease in four of the five nonsurvivors who died within 12 h after admission. In nonsurvivors the interval between appearance of petechiae and admission to the PICU was significantly shorter compared with survivors, indicating the importance of the time course of disease. We believe that if corticosteroid treatment is started after referral and admission on the intensive care unit therapy might only benefit a very small group of children. In that case, the time delay before initial corticosteroid treatment the infection process might have gone beyond any currently available therapeutic approach. Based on our data, however, we feel that a large randomized, double-blind, controlled study has to be designed to treat children with steroids as soon as possible after the first signs of disease. The results of this study might give an answer on the role of administration of steroids with in respect the time course of the disease.

During critical illness, cortisol has an important role on the metabolism of fatty acids, glucose, and protein (28). There is evidence to suggest that NEFAs may be the preferred fuel for oxidation in critical illness (29). In our study, we found on admission a positive correlation between levels of cortisol and NEFAs. Nonsurvivors had significant lower levels of NEFAs than survivors, indicating a lack of an adequate metabolic stress response in those who died. Nonsurvivors also showed significant lower levels of glucose, but there was no correlation with the levels of cortisol, indicating other mechanisms causing hypoglycemia (30).

In this study, we examined the ACTH/cortisol axis as an

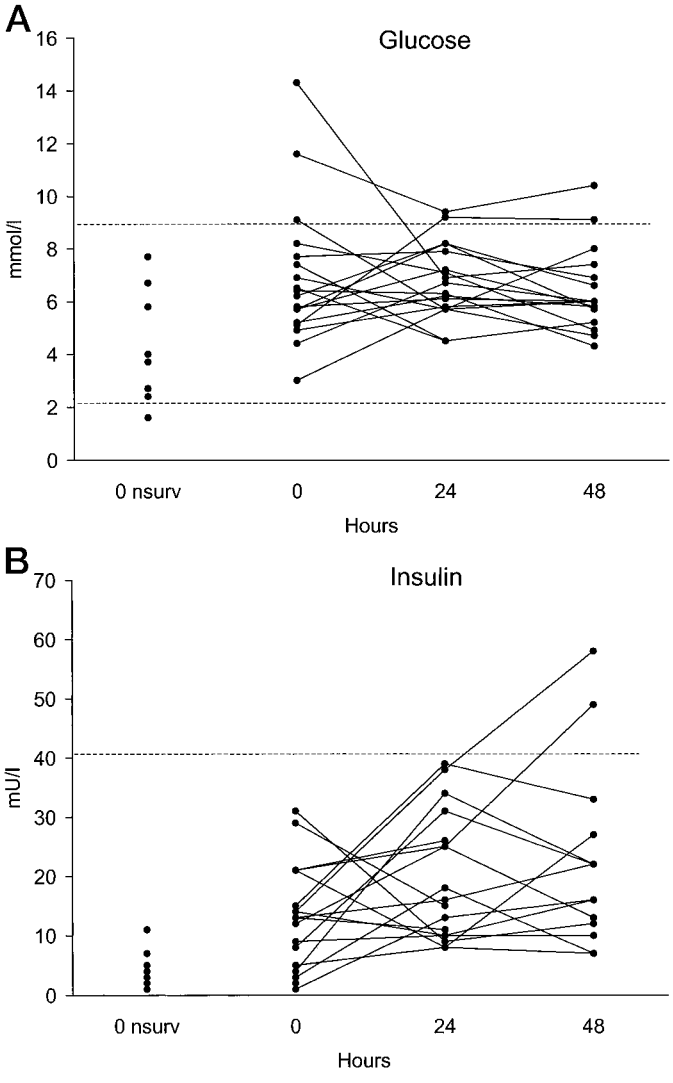

FIG. 4. Levels of insulin (B) and glucose (A) on admission for nonsurvivors (0 nsurv) and survivors (0) and the time course of these levels for survivors after 24 and 48 h. Reference values below or between *dotted lines*.

important modulator of cardiovascular and metabolic homeostasis during critical illness. We did not examine the serum concentrations of the catecholamines and glucagon that might have influenced the anabolic effects of insulin and GH. Preliminary data of a comparable group of children with meningococcal sepsis showed that nonsurvivors had significantly increased levels of GH and low levels of insulin-like growth factor I compared with survivors (manuscript in preparation). Research is in progress to assess the etiology and consequences of the alterations of the GH/insulin-like growth factor I axis.

Alterations in the thyroid axis in critically ill children are called "the euthyroid sick syndrome" (8–12). In our study, both survivors and nonsurvivors showed the features of "the euthyroid sick syndrome," decreased levels of T_3 and T_4, increased levels of rT_3, normal levels of fT_4, and no compensatory increased levels for TSH. Nonsurvivors, however, showed significantly higher T_3 levels and lower rT_3 levels compared with survivors. Low levels of T_3 and increased levels of rT_3 are explained by an adaptive mechanism aimed at preventing protein catabolism and lowering energy requirements in severely ill patients. It might, thus, be postulated that nonsurvivors are not able to adapt in the same way as survivors (31–34). The euthyroid sick syndrome may be mediated by cytokines and can be induced or aggravated by dopamine and glucocorticoids, whereas somatostatin may play a suppressive role (9, 28, 35–37.). In our study, 10 of the survivors received dopamine. Our study was not designed to study the immediate relation of thyroid function after dopamine withdrawal as done previously in children after cardiac surgery (28).

To get a better insight in the resolution of the hormonal and metabolic changes in children who survived, we evaluated the time course. Cortisol and ACTH levels in those who survived were on day 2 already significantly lower compared with the levels on admission and after 12 h. The cortisol and ACTH levels were within normal reference values, however, the circadian rhythm of cortisol was not seen. These findings suggest a persisting hyperactivity of the adrenal gland despite normalization of cortisol and ACTH levels. Furthermore, 2 days after admission levels of total T_4 remained unaltered, whereas levels of fT_4 and TSH increased but remained within normal reference values. Levels of rT_3 decreased and levels of T_3 and the T_3/rT_3 ratio increased, but all these levels still remained below normal reference values. These data indicate a slightly restoration but not a normalization of the thyroid function at day 2. Levels of NEFAs had decreased significantly at 2 days after admission, indicating that lipolysis had diminished. Levels of insulin and glucose showed a variable pattern within the normal range during the first 2 days after admission, which is in contrast to studies in critically ill adults where hyperglycemia and glucose intolerance with elevated insulin levels are hallmarks of stressed metabolism (38). Whether children with septic shock have a different insulin/glucose response compared with adults is not known. Although several hormonal axes and levels of NEFAs and lactate indicated the restoration of anabolism at the second day after admission, the urea nitrogen excretion did not change significantly and remained high. This is in accordance with studies in critically ill adult patients in which protein breakdown remained increased after the return to baseline values of the stress hormones and cytokines (39). In some studies of critically ill adult patients and critically ill children an improvement in protein synthetic rate or an improvement of nitrogen retention could be achieved by provision of exogenous nutrition (40–42). In our study, the provision of calories was far below the estimated need for calories during the first 2 days after admission (respectively, 45% and 42% too low). The low caloric supply might, therefore, be responsible for the high and unaltered excretion of nitrogen during these days in our patients.

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